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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,500	03/07/2002	Yusuke Amino	217637US0CONT	8895

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EXAMINER	
ZUCKER, PAUL A	

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,500	AMINO ET AL.	
	Examiner	Art Unit	
	Paul A. Zucker	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2004*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,24 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Current Status

1. This action is responsive to Applicants' amendment of 16 March 2004.
2. Receipt and entry of Applicants' amendment is acknowledged.
3. Claims 23, 24 and 26-28 are pending.
4. The indicated allowability of claim 24 is withdrawn in view of the new rejection below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Nofre et al (US 5,480,668 01-1996). Nofre discloses (Column 8, Table 1, entries 18 and 19) the compound N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. Nofre further discloses (Column 7, lines 24-51) a process for its synthesis and crystallization. The X-ray diffraction pattern of a crystalline compound is an inherent property of that compound.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) in view of Claude et al (US 5,510,508 04-1996).

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to reductive alkylation via hydrogenation in the presence of a catalyst followed by crystallization.

Nofre teaches (Column 8, Table 1, entries 18 and 19) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester and its unsaturated counterpart. Nofre further teaches (Column 7, lines 24-51) a general process for its synthesis. Nofre teaches a process for reductive alkylation of aspartame with the appropriate aldehyde (1.099 molar ratio aldehyde/aspartame) in methanol at room temperature for 24 hours. Nofre teaches removal of the reaction solvent (methanol), washing with aqueous HCl (to remove aspartame) and its

replacement with ethanol/water as a recrystallization solvent (solvent substitution). Aspartame as well as other impurities, is removed via the disclosed crystallization.

The difference between the process taught by Nofre and the instant process is that Nofre teaches a process for reductive alkylation which employs sodium cyanoborohydride as a reductant while the instant application claims the use of a catalytic hydrogenation reaction.

Claude, however, teaches (Column 3, line 63- column 4, line 26) a reductive alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame in methanol solution in the presence of platinum catalyst and hydrogen gas at 1 bar at room temperature.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The suggestion to combine is found in the nearly identical fields of invention. The motivation would have been to modify the general process for the synthesis of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester taught by Nofre by replacing his conditions for reductive alkylation with those taught by Claude. There would have been a reasonable expectation for success based on the fact that one equivalent hydrogenation process replaces another to produce the instant process.

Examiner's Response to Applicants' Remarks With Regard to This Rejection

7. Applicants present several arguments with regard to this rejection. The Examiner responds to these below:

a. Applicants argue that the cited references contain no disclosure or suggestion of such a crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. The Examiner disagrees. In fact, Nofre expressly teaches (Column 7, lines 61-67) that similar procedures to that disclosed for the synthesis of N-[N-[3,3-dimethylbutyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester are employed to give the compounds of Table 1 which includes the compound N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester which is at issue in this application. In the absence of some indication to the contrary on the part of Nofre, one of ordinary skill in the art would understand that Nofre thus teaches that the compounds of Table 1 are both crystalline and obtainable in such form by the method disclosed for N-[N-[3,3-dimethylbutyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

b. Applicants further argue that contrary to the assertion by the Examiner, this reference (Nofre) does not describe that the series of compounds appearing in Table 1 can be purified with the same or similar methods. The Examiner disagrees and directs Applicants' attention to the immediately preceding response.

c. Applicants argue that Nofre does not describe

(1) How the compound has been purified (how to purify);

(2) Whether or not the compound can be isolated in the crystalline form; or

(3) Even if the compound exists as a crystalline form.

The Examiner disagrees. Nofre provides a generic teaching for each of the items listed and further teaches that the generic teaching may be applied to each of the compounds in Table 1.

d. Applicants argue that the combination of Nofre and Claude fail to make a *prima facie* case for the synthesis of the instantly claimed compound since Nofre exemplifies the synthesis of N-[N-[3,3-dimethylbutyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. The Examiner disagrees. Nofre teaches a generic process, exemplified by the synthesis of N-[N-[3,3-dimethylbutyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, that is used to produce the instantly produced N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. Thus Nofre's teaching also extends to the instant aspartame derivative. One of ordinary skill in the art would have had no reason to expect the substitution of catalytic hydrogenation for the second step of the process would not be successful, especially given the well-understood generality of catalytic hydrogenation.

e. Applicants again argue that Nofre does not describe

(1) How the compound has been purified (how to purify);

(2) Whether or not the compound can be isolated in the crystalline form; or

(3) Even if the compound exists as a crystalline form.

In response, the Examiner directs Applicants' attention to his response above.

f. Applicants remarks with regard to a reasonable expectation for success have been addressed above.

g. Applicants argue that there is no disclosure of crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. The Examiner disagrees since such is clearly implied by Nofre.

h. Applicants characterize the generic teaching of Nofre as a "broad sweeping assertion". The Examiner disagrees since it is clearly limited to the compounds of Table 1. Thus no "leap of faith" is required as implied by Applicants.

i. Applicants again argue that the combination of Nofre and Claude fail to make a *prima facie* case for the synthesis of the instantly claimed compound since Nofre exemplifies the synthesis of N-[N-[3,3-dimethylbutyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. The Examiner again disagrees. Nofre teaches a generic process, exemplified by the synthesis of N-[N-[3,3-dimethylbutyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, that is used to produce the instantly produced N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. Thus Nofre's teaching also provides the suggestion to extend the modified process to the instant aspartame derivative as well.

j. Applicants present a paragraph excepted from the declaration of Professor Atwood. The Examiner has carefully considered Professor Atwood's conclusions but has found them unpersuasive. The Examiner finds that crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-

phenylalanine 1-methyl ester and the process for its production remain obvious over the disclosure of Nofre.

Applicant's arguments filed 16 March 2004have been fully considered but they are not persuasive for the reasons indicated above.

8. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) in view of Claude et al (US 5,510,508 04-1996).

Instantly claimed are a sweetening agent or sweetener comprising N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester produced by a process comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to reductive alkylation via hydrogenation in the presence of a catalyst followed by crystallization.

Nofre teaches (Column 8, Table 1, entries 18 and 19) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester and its unsaturated counterpart. Nofre further teaches (Column 7, lines 24-51) a general process for its synthesis. Nofre teaches a process for reductive alkylation of aspartame with the appropriate aldehyde (1.099 molar ratio aldehyde/aspartame) in methanol at room temperature for 24 hours. Nofre teaches removal of the reaction solvent (methanol), washing with aqueous HCl (to remove aspartame) and its replacement with ethanol/water as a recrystallization solvent (solvent substitution).

Aspartame as well as other impurities, is removed via the disclosed crystallization. Nofre further teaches (Column 10, lines 42-47, claims 6 and 7) the use of the compound of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester as a sweetening agent in combination with carriers or bulking agents.

The difference between the process taught by Nofre and the instant process is that Nofre teaches a process for reductive alkylation which employs sodium cyanoborohydride as a reductant while the instant application claims the use of a catalytic hydrogenation reaction.

Claude, however, teaches (Column 3, line 63- column 4, line 26) a reductive alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame in methanol solution in the presence of platinum catalyst and hydrogen gas at 1 bar at room temperature.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The suggestion to combine is found in the nearly identical fields of invention. The motivation would have been to modify the general process for the synthesis of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester taught by Nofre by replacing his conditions for reductive alkylation with those taught by Claude. There would have been a reasonable expectation for success based on the fact that one equivalent hydrogenation process replaces another to produce the instant process.

Examiner's Response to Applicants' Remarks With Regard to This Rejection

9. Applicants present no specific arguments with regard to this rejection but reference their arguments with regard to the previous rejection. In response, the Examiner references his responses thereto.

Declaration

10. The Declaration under 37 CFR 1.132 filed 3/16/2004 is insufficient to overcome the rejection of claims 23 and 26 based upon Nofre et al (US 5,480,668 01-1996) and Claude et al (US 5,510,508 04-1996) as set forth in the last Office action because: Declarant fails to set forth any facts which have bearing on the issues of the rejections of record. . The rejections of record can be overcome by a showing distinguishing the invention from the prior art.

Conclusion

11. Claims 23, 24 and 26-28 are pending. Claims 23, 24 and 26-28 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 571-272-0650. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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